5:15 p.m.

833-6 Effects of Cholesterol-Lowering Therapy and Antioxidant Vitamin Supplementation on the Risk of Stroke

Rory Collins, Jane Armitage, Sarah Parish, Peter Sleight, Richard Peto, for the MRC/BHF Heart Protection Study Collaborative Group, *Clinical Trial Service Unit, Oxford University, Oxford, United Kingdom.*

Background: Previous randomized trials have involved too few strokes to assess the effects of cholesterol lowering, and of antioxidant vitamins, reliably.
Methods: A wide range of people at increased risk of coronary and other occlusive vascular events were randomly allocated to receive 40 mg simvastatin daily, or matching placebo tablets, for an average of at least five years. In addition, using a factorial design, half of the patients were randomly allocated active antioxidant vitamins (600 mg E, 250 mg C, 20 mg beta-carotene daily) and half allocated placebo vitamin capsules.
Results: Between July 1994 and May 1997, 20,536 people aged 40-80 years were recruited. Of these, 9,845 were aged <65y, 4,889 were aged 65-69y, and 5,802 were aged 70-80y. Previous myocardial infarction was reported at entry by 8,510 patients (most of whom were elderly, female or with "low" blood cholesterol), 4,869 had some other history of coronary heart disease (CHD), 3,280 had cerebrovascular disease, 6,748 had some other peripheral arterial disease and 5,963 had diabetes mellitus (with overlap between some of these categories). Allocation to 40 mg daily simvastatin has produced average reductions during the study of about 45 mg/dl in LDL-cholesterol. About 1,500 strokes are expected before scheduled follow-up is completed in October 2001.
Conclusion: This study will provide the first large-scale prospective evidence as to whether reducing LDL cholesterol, and supplementing antioxidant vitamins, reduces the risk of stroke.

ORAL CONTRIBUTIONS

834 Arterial Remodeling: Basic and Clinical

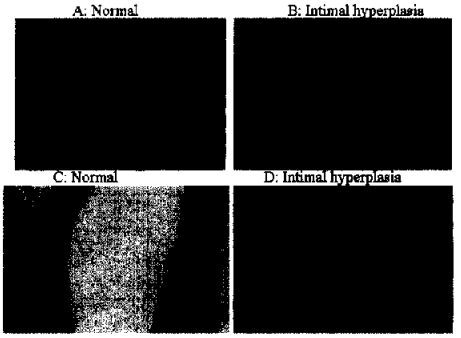
Monday, March 18, 2002, 4:00 p.m.-5:30 p.m.
Georgia World Congress Center, Room 160W

4:00 p.m.

834-1 Dedifferentiation of Vascular Smooth Muscle Cells Involved in Remodeling of Small Intramyocardial Coronary Arteries Distal to a Flow-Limiting Epicardial Coronary Artery Stenosis

Huashan Hong, Sergei Aksenov, Xiaoming Guan, Joseph Marrak, David Waters, John T. Fallon, Chunguang Chen, *Newark Beth Israel Medical Center, Newark, New Jersey, Mount Sinai School of Medicine, New York, New York.*

We previously described intimal hyperplasia and lumen narrowing of small intramyocardial coronary arteries (SIMCA) in ischemic myocardium distal to a flow-limiting epicardial coronary stenosis (CS). To test whether changes in intermediate filament (IF) proteins of vascular smooth muscle cells might contribute to SIMCA remodeling, we mapped by immunochemistry IF in vascular smooth muscle cells of SIMCA in normal and ischemic regions. Methods: Group 1: 10 pigs with 4-week severe CS to reduce resting coronary flow by ~30%; Group 2: 8 control pigs without CS. Wall thickness (WT) and lumen diameter (LD) of SIMCA were measured; %LD (LD/[2WT+LD]) was calculated to assess the severity of SIMCA lumen narrowing. Antibodies targeted at the IF proteins desmin, vimentin and cytokeratin were used for immunohistological evaluation. Results: %LD of SIMCA decreased in Group 1 vs 2 (17±15% vs 38±13%, p<0.05). In normal SIMCA walls (Group 2), cytokeratin and desmin expression were scanty (Figure A & C), but in ischemic SIMCA walls (Group 1), cytokeratin expression was markedly increased (Figure B, p<0.01) and desmin markedly decreased (Figure D, p<0.01). No difference in vimentin staining was found between the groups. Conclusion: Intimal hyperplasia and lumen narrowing in small intramyocardial coronary artery were associated with significant alterations of intermediate filaments, indicating dedifferentiation of vascular smooth muscle cells in the SIMCA wall.

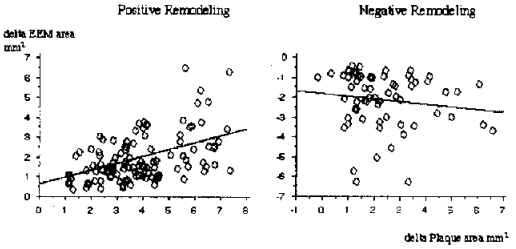


4:15 p.m.

834-2 Negative Remodeling Frequently Occurs in Mildly Stenotic Native Coronary Lesions and Is Unrelated to Plaque Size

Paul Schoenhagen, William A. Magyar, Samir R. Kapadia, Khalid M. Ziada, Hiroshi Tsutsui, Showkat A. Haji, Jon Klingensmith, Steven E. Nissen, Murat E. Tuzcu, *The Cleveland Clinic Foundation, Cleveland, Ohio.*

Background: Positive and negative arterial remodeling describes the expansion and shrinkage of the external elastic membrane (EEM) area at atherosclerotic lesion sites. In mildly stenotic lesions positive remodeling accommodates plaque growth without luminal compromise. Negative remodeling in these lesions is incompletely described.
Methods: We analyzed intravascular ultrasound data of 251 native coronary vessels with mildly stenotic focal lesions (50% or less diameter stenosis by angiography). At the lesion and proximal reference site EEM area, lumen area, and plaque area were determined. The differences of the plaque area (deltaPA) and EEM area (deltaEEM) between proximal reference and lesion site were calculated. The Remodeling index (RI) was calculated by dividing the EEM area at the lesion and proximal reference site. Positive and negative remodeling was defined as a RI of 1.05, and 0.95, respectively.
Results: Positive remodeling was found in 116 lesions (46%) and negative remodeling in 66 (26%). Plaque and lumen area were significantly larger in lesions with positive than negative remodeling (p=0.04 and 0.0019) A significant correlation between deltaEEM and deltaPlaque area was found for positive but not for negative remodeled lesions (R=0.50, p<0.0001 and 0.14, p=0.29)
Conclusion: These results demonstrate that negative remodeling frequently occurs in mildly stenotic lesions of native coronary artery disease, is unrelated to plaque size, and contributes to luminal stenosis.



4:30 p.m.

834-3 The Role of Adventitia in Coronary Atherosclerosis: Results of Echocardiographic Imaging of the Left Anterior Descending Coronary Artery

Irmina Gradus-Pizlo, Brian Bigelow, Yousuf Mahomed, Stephen G. Sawada, Karen Rieger, Harvey Feigenbaum, *Indiana University School of Medicine, Indianapolis, Indiana.*

Background, High-frequency, two-dimensional transthoracic echocardiography (HR-2DTTE) measurements of left anterior descending coronary artery (LAD) wall thickness are similar to measurements obtained by magnetic resonance imaging, but larger than measurements obtained by intravascular ultrasound. We hypothesize that this difference is due to inclusion of adventitia by HR-2DTTE imaging of the LAD, and that adventitia must be increasing in thickness with the development of atherosclerosis. We evaluated the contribution of adventitia to the wall thickness of the normal and atherosclerotic LAD imaged by HR-2DTTE using high-frequency epicardial echocardiography (HFEE) as the reference standard.
Methods, Eighteen patients (10 men, mean age 62, 13 with coronary atherosclerosis [CA], 5 with normal coronary arteries [NL]) referred for open-heart surgery underwent pre-operative HR-2DTTE evaluation of the LAD (SONOS 5500; 3-8MHz transducer) and intra-operative HFEE of the LAD (SONOS 5500; 7-15MHz transducer).
Results, Wall thickness was greater in CA than in NL patients by both HR-2DTTE (1.9mm±0.3 vs. 1.0mm±0.1; p=10-5) and HFEE (1.8mm±0.2 vs. 1.0mm±0.2; p=10-6). On HFEE the average intima/media thickness was greater in CA than in NL patients (0.78mm±0.3 vs. 0.34mm±0.1, p=0.005). The average thickness of adventitia was also greater in CA than in NL patients (0.92mm±0.2 vs. 0.54mm±0.2, p=0.0005). HR-2DTTE and HFEE measurements of the wall thickness correlated well (r=0.83 reader 1,p<0.001 and r=0.61 reader 2,p<0.01).
Conclusions, Adventitia represents a major portion of the LAD wall thickness imaged by HR-2DTTE and HFEE and increases in thickness significantly with the development of atherosclerosis. HR-2DTTE provides accurate, noninvasive measurements of total LAD wall thickness.